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Date October 10, 2003	From: Richard M. Lebovitz (jmj)
To: Examiner Patricia A. Patten Facsimile No.: 703-872-9306 Telephone No.:	MILLEN, WHITE, ZELANO & BRANIGAN, P.C. Arlington Courthouse Plaza I 2200 Clarendon Blvd., Suite 1400 Arlington, VA 22201 (U.S.A.) (Fax: 703-243-6410) Writer's Direct Dial: (703) 812-5317 Writer's Internet Address:
RE: Application No. 09/891,526 Our reference: UROMED-1	
Total No. of Pages 17; if you do not receive all pages, please call 703-243-6333.	

OFFICIAL RESPONSE

IN THE UNITED STATES PATENT AND TRADEMARK OFFICE

In re Application of:

Martin G. CROSBY

Examiner: Patricia A. Patten

Serial No.: 09/891,526

Group Art Unit: 1651

Filed: June 27, 2001

Title: COMPOSITIONS AND METHODS FOR ENHANCING OR TREATING FEMALE SEXUAL RESPONSE (As Amended)

DECLARATION UNDER §1.132

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Commissioner for Patents
P.O. Box 1450
Alexandria, VA 22313-1450

I, Martin G. Crosby, RPh., being duly warned, declare that:

1. I am a citizen of the United States, residing in Charleston, South Carolina. I am inventor of the above-identified application and also the President and owner of QualiLife Pharmaceuticals, Inc., the application assignee

2. The attached publication (Ferguson et al., *J Sex Marital Ther.*, 29:33-44, 2003, Exhibit 1) describes a randomized, double-blinded, placebo-controlled cross-over study to evaluate the efficacy and safety of a composition ("Zestra") of the claimed invention. I am co-author of the publication, and attest to the accuracy of the results obtained therein.

3. The composition evaluated in the study comprised borage seed oil, Angelica root, Coleus forskohlii, and several excipients. See, Ferguson et al., Page 34. This combination is disclosed in the application as originally filed. See, e.g., original Claim 2.

4. Evening primrose oil is also present in the composition. See, Ferguson et al., Page 34. As stated in the specification, both evening primrose and borage seed oil are sources of gamma linolenic acid ("GLA").

a) "GLA is found predominantly in the seed of the Borage plant, but is also found in evening primrose seed oil and other botanical and natural sources." Specification, Page 2, lines 15-17.

b) "In addition to borage seed oil, other sources of GLA can be utilized, including, e.g., purified or isolated GLA, botanical extracts, such as evening primrose oil (e.g., *Oenothera biennis* and *Oenothera lamarckiana*), black currant oil, spirulina, oils from the seeds of the Ribes family, etc." Specification, Page 2, lines 28-31.

c) " . . borage seed oil and/or evening primrose oil ... " Specification, Page 10, lines 21-22.

d) "Example 1. Preparation of base oil . (Optionally, in some cases, primrose oil (e.g., 9% GLA content) was added to the base oil ...)." Specification, Page 14, lines 11-13.

5. According to the publication:

a) "Both normal and FSAD women showed statistically significant improvements, relative to placebo, in level of arousal, genital sensation, and ability to have orgasms, and sexual pleasure." Ferguson et al., Page 34, lines 3-6.

b) See, also Ferguson et al., Page 38-42, "Efficacy," for a more detailed description of the data.

6. Thus, these results clearly establish that a composition of Claim 35 is effective as claimed.

I hereby declare that all statements made herein of my own knowledge are true and that all statements made on information and belief are believed true; and further that these statements were made with the knowledge that willful false statements and the like so made are punishable by fine or imprisonment, or both, under section 1001 of Title 18 of the United States Code, and that such willful false statements may jeopardize the validity of the application or any patent issuing thereon.

_____ _____

Date Martin G. Crosby, R.Ph.

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10-10-03
Date

Martin G. Crosby, R.Ph.
Martin G. Crosby, R Ph.

EXHIBIT 1

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Randomized, Placebo-Controlled, Double Blind, Crossover Design Trial of the Efficacy and Safety of *Zestra for Women* in Women With and Without Female Sexual Arousal Disorder

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Zestra for Women™ is a botanical feminine massage oil formulated to enhance female sexual pleasure and arousal when applied to the vulva. We conducted this randomized, double-blinded, crossover study to evaluate the efficacy and safety of Zestra for Women compared to placebo oil in 10 women with and 10 women without female sexual arousal disorder (FSAD) in conditions of home use in conjunction with sexual activities. Subjects were screened by physical examination, sex therapist interviews, and questionnaires. We randomized qualified subjects to treatment paths and gave them 5 doses of test article and diaries to use at home. At Visit 2, we assessed them by questionnaires and gave them 5 doses of crossover test article and diaries to use at home. At the final visit, we assessed them with questionnaires. We assessed safety by adverse event reports and primary efficacy by responses to a diary question regarding satisfaction with arousal. Secondary efficacy instruments included remaining diary questions, recall-based questionnaires, global assessment questions, and a consumer-testing questionnaire.

Test articles provided by QualiLife Pharmaceuticals, Inc., Sixty-one Medical Center, 1483 T. Gadson Blvd, Ste 105, Charleston, SC 29407. Authors Ferguson, Steidle, Singh, Alexander, and Weihmiller have no financial interest in QualiLife Pharmaceuticals and did not receive any financial compensation for their contributions to this study. Author Crosby is owner of QualiLife Pharmaceuticals.

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All 20 subjects completed the study. Three subjects reported single incidences of mild genital burning sensations lasting 5–30 min after use of Zestra for Women. Both normal and FSAD women showed statistically significant improvements, relative to placebo, in level of arousal, level of desire, satisfaction with arousal, genital sensation, ability to have orgasms, and sexual pleasure. Although FSAD women showed greater magnitude of response, the presence of FSAD had no effect on response rates. Zestra for Women was just as effective in women using selective serotonin reuptake inhibitor antidepressants as in women not using antidepressants. Zestra for Women improved sexual function in normal and FSAD women under conditions of home use.

Zestra for Women is a botanical feminine massage oil formulated to enhance female sexual pleasure, to increase warmth, sensitivity, sensation, and to facilitate arousal when applied to the clitoris, labia, and vaginal opening. Zestra for Women is not a drug but has been developed under the U.S. Cosmetics Act. This product is not intended to diagnose, treat, cure, or prevent any disease and has not been evaluated by the Food and Drug Administration (FDA). The ingredients are a proprietary blend of borage seed oil, evening primrose oil, Angelica root extract, Coleus forskohlii extract, ascorbyl palmitate, dl-alpha tocopherol, and natural fragrances. The components in this mixture are available in the United States as dietary supplements, or as ingredients in foods or cosmetics and are on the FDA's generally recognized as safe list. The borage and evening primrose oils contain high amounts of gamma-linolinic acid, which is metabolized in the skin to prostaglandin E_1 (Dines, Cotter, & Cameron, 1996). This process is generally recognized to cause increased blood flow and nerve conduction. Angelica root extract contains osthole, which increases cGMP and cAMP, nonspecifically (Teng, Lin, Ko, Wu, & Huang, 1994). Coleus forskohlii extract contains forskolin, coleonol, and related diterpenes, which are adenylate cyclase stimulants (Andersson & Stief, 1997).

Female sexual dysfunction (FSD) includes a number of disorders: hypoactive sexual desire disorder, sexual aversion disorder, sexual arousal disorder, orgasmic disorder, and several sexual pain disorders. Although these disorders may frequently have overlapping and interdependent subjective and physiological components, it appears most fruitful to focus an intervention on one particular disorder (Ferguson, 2002). The definitions of the International Consensus Development Conference on Female Sexual Dysfunction: Definitions and Classifications (Basson et al., 2000) are structured to provide a description of the subjective and/or physiologic characteristics of the disorders as well as the caveat that the condition must cause personal distress. The Consensus Conference definition of female sexual arousal disorder (FSAD) is "the persistent or recurrent inability to attain or maintain

sufficient sexual excitement, causing personal distress. It may be expressed as a lack of subjective excitement or a lack of genital (lubrication/swelling) or other somatic responses" (Basson et al., 2000, p. 90). The etiology of FSAD is poorly understood. Iatrogenic FSAD can be linked to a variety of surgical procedures and medications. Additionally, antidepressants of the selective serotonin reuptake inhibitor class (SSRIs) are well known to decrease sexual desire, arousal, orgasms, and sexual pleasure.

This study was conducted to evaluate the efficacy and safety of Zestra for Women compared to placebo oil in women with and without FSAD in conditions of home use in conjunction with sexual activities. The effect of SSRI antidepressant usage on the outcome was examined.

METHODS

Design

Zestra for Women was studied in ten women with FSAD and ten normal women in a double-blinded, placebo-controlled, two-way crossover design. We matched placebo to the active test article based on viscosity, fragrance, color, absorbency, and lubricity. At the screening visit, each subject who signed an informed consent form was interviewed by a sex therapist, underwent a physical examination, and completed the Female Sexual Function Index (FSFI; Rosen et al., 2000) and the Female Sexual Distress Scale–20 (FSDS®, Derogatis, 2000). Each woman was assigned to the normal or FSAD group based on the results of the interview and the FSDS score (range 0 to 80). Normal women were allowed no interview evidence of any FSD and were required to have an FSDS score of less than 40. Women assigned to the FSAD group were allowed to have evidence of desire disorder and orgasmic disorder, but their chief complaint was required to be FSAD. Women with pain disorders and women with FSDS scores greater than 60 were excluded from participation. Subjects were randomized to treatment paths, given five 1-ml doses of test article, and instructed in the use of the diary, the Female Sexual Encounter Profile (FSEP®; Ferguson, 2002). Subjects were to return to the clinic for Visit 2 after completing five usages of the test article at home. At Visit 2, they completed the FSFI, the FSDS, two global assessment questions (GAQs), and the QualiLife Consumer Testing Survey (QCTS). We gave them five 1-ml doses of the crossover test article and provided them with five additional diaries. At the final visit, Visit 3, subjects again completed the FSFI, the FSDS, the GAQ, and the QCTS.

Inclusion/Exclusion Criteria

On the basis of an interview by the sex therapist, we diagnosed subjects as "normal" or FSAD. Subjects were one of the following: postmenopausal,

using hormonal contraception for at least three months prior to study entry, able to document that they had undergone tubal ligation at least three months prior to study entry, or with a vasectomized partner. FSAD subjects were required to have previously been fully functional, to have currently demonstrated a score between 40 and 60 on the FSDS, and to be willing to attempt sexual activities at least three times weekly. Normal subjects were required to have an FSDS score of less than 40. Exclusion criteria included unresolved sexual trauma or abuse; primary anorgasmia, vaginismus, sexual pain disorder, or sexual aversion disorder, pregnancy or nursing, currently active moderate-to-severe vaginitis, use of neuroleptics or lithium or bupropion within previous three months; and any condition that, in the investigator's opinion, would endanger the subject, would interfere with the subject's ability to provide informed consent or to comply with study instructions, or would confound the interpretation of the study results. Subjects were not excluded because of antidepressants, nutritional supplements, or hormonal replacement therapy. We made a specific effort to recruit equal numbers of normal and FSAD subjects who were using and who were not using antidepressants of the SSRI class.

Endpoints

We assessed safety by monitoring adverse events (AEs). The primary efficacy variable was the number of successes (satisfaction with sexual arousal as indicated by yes responses to FSEP diary question 3) divided by the number of valid attempts (FSEP Q7). The secondary efficacy parameters were the responses to the global assessment questions, to the remaining diary questions, to the FSFI, to the FSDS, and to the quantitative questions from the QCTS. We employed paired-*t* analyses in order to assess treatment effects for each subject compared to placebo effects. We assessed sequence and carryover period effects using group mean comparisons of the primary efficacy variable. We assessed responsiveness of the normal versus the FSAD subjects by calculating the percentage of subjects that showed an improvement (Zestra minus placebo) in GAQ question 2. We analyzed the effect of SSRI usage on efficacy by using Student's *t*-test (group mean comparisons, adjusted for unequal variance) of SSRI subject responses to no-SSRI subject responses.

The following hypotheses were the objectives of this study.

1. Zestra for Women increases arousal in women with FSAD.
2. Zestra for Women increases arousal in normal women.
3. Zestra for Women improves other sexual function endpoints.
4. Zestra for Women improves sexual function in women regardless of presence or absence of FSAD.
5. Zestra for Women is efficacious in the presence of SSRI antidepressants.
6. Zestra for Women is safe under these conditions of usage.

RESULTS

Demographics

Twenty caucasian women (ages 31 to 57 years) participated in this study Table 1 shows that the normal and FSAD subjects were similar in all respects except sexual function parameters for desire, arousal, lubrication, orgasm, and distress.

TABLE 1. Baseline Demographics

Descriptor	Normals (mean ± *SD*, range or incidence)	FSAD (mean ± *SD*, range or incidence)	*p* (*t*, unequal variance)
Age (years)	43.2 ± 5.7 31–50	44.4 ± 8.7 33–57	0.7020
Height (cm)	166.4 ± 6.6 153.7–177.8	165.8 ± 4.1 157.5–171.5	0.8197
weight (kg)	76.3 ± 17.8 57.2–115.4	78.7 ± 18.6 54.4–101.6	0.7702
Menarche (years)	12.7 ± 2.1 10–17	13.1 ± 1.1 11–14	0.5944
1st Intercourse (years)	18.3 ± 2.0 15–22	17.6 ± 2.7 15–24	0.6469
Postmenopausal	4/10	3/10	NA
HRT	3/10	3/10	NA
Hormonal contraception	1/10	4/10	NA
SSRIs	3/10	4/10	NA
Race Caucasian	10/10	10/10	NA
FSFI desire	4.1 ± 0.9 3.0–6.0	2.3 ± 1.4 1.2–5.4	0.0030445
FSFI arousal	5.0 ± 0.8 3.0–6.0	2.5 ± 0.9 1.2–3.9	0.0000057
FSFI lubrication	5.6 ± 0.8 3.6–6.0	4.3 ± 1.7 1.8–6.0	0.0311487
FSFI orgasm	4.9 ± 1.5 1.2–6.0	2.6 ± 1.3 1.2–5.2	0.0019216
FSFI satisfaction	5.2 ± 1.2 2.4–6.0	3.4 ± 0.5 2.4–4.0	0.0005111
FSFI pain	6.0 ± 0.0 6.0–6.0	5.8 ± 0.5 4.8–6.0	0.1509505
FSFI total	30.7 ± 3.0 26.6–36.0	20.9 ± 4.5 15.0–28.1	0.0000124
FSDS	11.2 ± 7.9 1–25	45.2 ± 5.0 41–57	0.0000000011

Note. HRT = hormone replacement therapy, FSFI = Female Sexual Function Index (Rosen et al., 2000), FSDS = Female Sexual Dysfunction Scale–20 (Derogatis, 2000)

Safety

All 20 subjects completed the study. Three subjects reported single incidences of mild genital burning sensations of 5–30 minutes duration while using Zestra. One subject reported several incidences of vaginal irritation associated with coitus while using placebo. She was subsequently diagnosed and treated for a yeast infection. Two AEs that were reported by those receiving the placebo treatment were considered unrelated to the test article: fatigue associated with hypothyroidism, and a sinus infection.

Efficacy

There was no statistical evidence of either sequence or carryover effects. Table 2 shows the mean changes in responses for the FSEP, FSFI, FSDS, GAQ, and for the quantitative questions from the QCTS for both subject groups. The primary efficacy variable, FSEP Q3, which assesses satisfaction with level of arousal, has a range of 0 to 1. Normal subjects had a mean score of 0.730 ± 0.297 while on placebo and a mean score of 0.950 ± 0.158 while on Zestra. The mean improvement in the FSEP Q3 score was 0.220 ± 0.277, which was statistically significant ($p = 0.0333$) by paired-t analysis. FSAD subjects had a mean score of 0.287 ± 0.337 while on placebo and a mean score of 0.855 ± 0.315 while on Zestra. Their mean improvement in the FSEP Q3 score was 0.568 ± 0.360, which was statistically significant ($p = 0.00074$) by paired-t analysis.

Secondary efficacy variables included FSEP questions 2, 4, 5, and 6, as well as an FSEP total score (sum of Q2–Q6). FSEP Q2 assesses level of desire and has a range of 0 to 3. Highly significant improvements in this diary-based desire variable were seen in both normal subjects ($p = 0.00041$) and FSAD subjects ($p = 0.00011$). FSEP Q4 asks if the subject had lubrication sufficient to allow comfortable intercourse (even if intercourse did not actually occur). Neither normal nor FSAD subjects showed significant changes in FSEP Q4. The FSAD subjects showed a statistically significant ($p = 0.013$) increased frequency of orgasms (FSEP Q5), but the normal subjects failed to reach significance ($p = 0.053$). FSEP Q6 assesses level of arousal and has a range of 0 to 3. Normal subjects showed a significant ($p = 0.0063$) increase in level of arousal as did the FSAD subjects ($p = 0.00091$). FSEP total (range = 0–9) was significantly increased in normal subjects ($p = 0.0027$) and in FSAD subjects ($p = 0.00012$).

The FSFI provides six factored domain scores, with a maximum score of 6 for each domain. Additionally, a total score (maximum = 36) is calculated. Higher scores indicate a more "healthful" condition. The domains are desire, arousal, lubrication, orgasm, satisfaction, and pain. Zestra produced significant improvements in the arousal domain in normal subjects and in the arousal, orgasm, and satisfaction domains and the FSFI total score in the FSAD subjects. There were no deleterious changes in either subject group.

TABLE 2. Mean Changes in Efficacy Parameters

Endpoint	Normals mean change (Zestra − placebo) ± *SD*, *p* (paired *t*)	FSAD mean change (Zestra − placebo) ± *SD*, *p* (paired *t*)	Pooled normal and FSAD mean change (Zestra − placebo) ± *SD*, *p* (paired *t*)
FSEP Q5 satisfaction with arousal	0.22 ± 0.28 0.033	0.57 ± 0.36 0.000074	0.39 ± 0.36 0.001
FSEP Q2 level of desire	0.51 ± 0.30 0.00041	0.83 ± 0.40 0.00011	0.67 ± 0.38 0.0000002
FSFP Q4 adequate lubrication	0.08 ± 0.25 0.34	0.01 ± 0.17 0.17	0.08 ± 0.21 0.10
FSFP Q5 orgasm attained	0.150 ± 0.21 0.053	0.29 ± 0.30 0.013	0.22 ± 0.26 0.0014
FSEP Q6 level of arousal	0.35 ± 0.52 0.0063	0.92 ± 0.60 0.00091	0.65 ± 0.55 0.000056
FSEP total	1.51 ± 1.01 0.0027	2.69 ± 1.35 0.00012	2.00 ± 1.35 0.000002
FSFI desire	−0.30 ± 1.50 0.58	0.60 ± 1.39 0.20	0.15 ± 1.27 0.60
FSFI arousal	0.728 ± 0.79 0.018	1.53 ± 1.46 0.0090	1.13 ± 1.22 0.00056
FSFI lubrication	0.48 ± 0.97 0.15	0.72 ± 1.54 0.17	0.60 ± 1.26 0.047
FSFI orgasm	0.72 ± 1.10 0.068	1.44 ± 1.41 0.010	1.08 ± 1.29 0.0015
FSFI satisfaction	−0.20 ± 1.25 0.65	1.20 ± 1.29 0.017	0.50 ± 1.43 0.14
FSFI pain	−0.08 ± 0.25 0.34	0.2 ± 0.43 0.18	0.06 ± 0.37 0.48
FSFI total	1.34 ± 3.39 0.24	5.69 ± 5.10 0.0064	3.52 ± 4.77 0.0038
FSDS	−1.50 ± 10.1 0.65	−8.80 ± 19.27 0.18	−5.15 ± 15.41 0.15
GAQ 1	1.70 ± 1.25 0.0020	2.10 ± 1.66 0.0031	1.90 ± 1.50 0.000012
GAQ 2	1.60 ± 1.17 0.0020	2.20 ± 1.23 0.00031	1.90 ± 1.21 0.0000011
QCTS Q1 sensation	0.90 ± 0.57 0.00073	1.10 ± 0.57 0.00017	1.00 ± 0.56 0.0000002
QCTS Q6 pleasure	0.70 ± 0.48 0.0015	0.70 ± 0.48 0.0013	0.70 ± 0.47 0.000002
QCTS Q7 lubrication	0.20 ± 0.79 0.44	0.30 ± 0.48 0.081	0.25 ± 0.64 0.096
QCTS Q8 orgasm	0.40 ± 0.52 0.037	0.50 ± 0.48 0.081	0.25 ± 0.64 0.096
QCTS Q9 enhanced experience	1.30 ± 1.60 0.0063	1.50 ± 0.85 0.00034	1.40 ± 0.99 0.0000048
QCTS Q10 purchase	2.35 ± 2.16 0.0010	4.50 ± 2.49 0.00029	3.88 ± 2.36 0.00000059
QCTS Q12 price	2.55 ± 3.25 0.04994	2.60 ± 3.26 0.033	2.46 ± 3.17 0.0026

Note. FSEP = Female Sexual Encounter Profile (Ferguson, 2004); FSDS = Female Sexual Distress Scale—20 (Derogatis, 2000). GAQ = global assessment questions; QCTS = Quality of Life Consumer Testing Survey

The FSDS is a 20-question instrument with a range of 0 to 80. A lower score indicates a less distressed situation. Although Zestra produced decreases in both groups, no change was significant

The GAQs that we used were: GAQ 1 "While using the study medication, did you feel that your level of sexual arousal (excitement) improved?" (0 = Not at all, 1 = A little, but barely noticeable; 2 = Somewhat, 3 = Quite, 4 = Greatly). GAQ 2 "While using the study medication, did you feel that your sexual pleasure was enhanced? (0 = Not at all; 1 = A little, but barely noticeable; 2 = Somewhat, 3 = Quite, 4 = Greatly). Zestra produced strong and very significant improvements in the scores for each question in both groups The response rates for the normal and for the FSAD groups were 80% and 90%, respectively.

The QCTS consists of twelve questions intended to assess users' responses and attitudes regarding the product Questions 1, 6, 7, 8, 9, 10, and 12 are quantitative. Question 1 assesses genital sensation. Question 6 assesses pleasure associated with sexual activities Question 7 assesses lubrication. Question 8 addresses enhancement of ability to have orgasms. Question 9 addresses enhancement of sexual experiences Question 10 addresses willingness to purchase the product Question 12 asks subjects how much they would pay for the product. Both normal and FSAD subjects showed significant improvements (over placebo) in sensation, pleasure, enhancement of sexual experiences, willingness to purchase the product, and the price they would pay for the product.

Since Zestra for Women produced significant improvements in the primary efficacy variable for both normal and FSAD subjects, the data for both groups were pooled and then tested by paired t tests to determine if the presence or absence of FSAD made any difference in the outcome. The right column of Table 2 shows the pooled mean changes with standard deviations and the p calculated from the paired t tests. In most variables, the significance increased The normal group showed significant improvements in 13 of 23 efficacy variables, the FSAD group showed significant improvements in 17 of 23 efficacy variables, the pooled group showed significant improvements in 17 of 23 variables The FSFI lubrication domain became significant, whereas the FSFI satisfaction domain, which was significant in the FSAD group, failed to reach significance when the groups were pooled Overall, the outcome was not affected by pooling normal and FSAD data. The response rate for all 20 women participating in the study was 85%.

We examined the effect of SSRI usage on the efficacy response to Zestra for Women by comparing data from those who used SSRI antidepressants (7 subjects) to those who did not (13 subjects), without regard to the subjects' classification as normal or FSAD. Table 3 shows the mean changes in the efficacy parameters for both groups and the results of mean group comparisons of the changes There were no significant differences in responses between the no-SSRI group and the SSRI group Both the no-SSRI group and the SSRI group showed significant improvements in the primary efficacy

TABLE 3. Effect of SSRI Usage on Mean Changes in Efficacy Parameters

Endpoint	No SSRI mean change (Zestra − placebo) ± *SD*, *p* (paired *t*)	SSRI mean change (Zestra − placebo) ± *SD*, *p* (paired *t*)	*p* (*t*, group mean comparison)
FSEP Q3 satisfaction with arousal	0.40 ± 0.39 0.0028	0.38 ± 0.53 0.025	0.89
FSEP Q2 level of desire	0.59 ± 0.39 0.00014	0.83 ± 0.34 0.00067	0.17
FSEP Q4 adequate lubrication	0.06 ± 0.15 0.17	0.11 ± 0.50 0.36	0.68
FSEP Q5 orgasm attained	0.20 ± 0.29 0.028	0.26 ± 0.65 0.022	0.63
FSEP Q6 level of arousal	0.55 ± 0.59 0.0053	0.78 ± 0.48 0.0048	0.56
FSEP total	1.80 ± 1.44 0.00071	2.36 ± 1.17 0.0018	0.37
FSFI desire	0.14 ± 1.39 0.73	0.17 ± 1.13 0.70	0.96
FSFI arousal	1.08 ± 1.28 0.010	1.20 ± 1.17 0.035	0.84
FSFI lubrication	0.62 ± 1.54 0.12	0.56 ± 1.21 0.27	0.91
FSFI orgasm	1.02 ± 1.55 0.019	1.20 ± 1.24 0.04	0.76
FSFI satisfaction	0.52 ± 1.68 0.28	0.46 ± 0.94 0.24	0.91
FSFI pain	0.09 ± 0.47 0.49	0.0 ± 0.0 NA	0.49
FSFI total	3.48 ± 5.47 0.041	3.59 ± 3.49 0.035	0.96
FSDS	−6.2 ± 14.9 0.16	−1.5 ± 14.5 0.64	0.72
GAQ 1	1.69 ± 1.54 0.0020	2.29 ± 1.25 0.0029	0.37
GAQ 2	1.77 ± 1.17 0.00014	2.14 ± 1.56 0.0056	0.55
QCTS Q1 sensation	0.85 ± 0.55 0.00014	1.29 ± 0.49 0.00045	0.089
QCTS Q6 pleasure	0.69 ± 0.48 0.00022	0.71 ± 0.49 0.0082	0.92
QCTS Q7 lubrication	0.15 ± 0.69 0.44	0.45 ± 0.53 0.078	0.34
QCTS Q8 orgasm	0.23 ± 0.44 0.082	0.57 ± 0.53 0.050	0.18
QCTS Q9 enhanced experience	1.23 ± 1.01 0.00090	1.71 ± 0.95 0.0031	0.51
QCTS Q10 purchase	3.55 ± 2.51 0.00022	4.86 ± 2.29 0.0014	0.18
QCTS Q12 price	2.15 ± 3.12 0.050	3.07 ± 3.42 0.055	0.56

Note. FSEP = Female Sexual Encounter Profile (Ferguson, 2002); FSFI = Female Sexual Function Index (Rosen et al., 2000); GAQ = global assessment questions; QCTS = Quality Consumer Testing Survey

parameter and in 14 of 22 secondary efficacy parameters. The response rates for no-SSRI and the SSRI groups were 85% and 86%, respectively.

DISCUSSION

This study is a landmark in testing nondevice products in women with FSAD. This is the first well-designed, well-controlled study to show positive results in at-home conditions using a diary to record the outcome of actual sexual encounters. The primary efficacy variable, FSEP Q3, directly addresses the critical question established in FDA guidelines for drug products pursuing an indication in FSAD (U.S. FDA, 2000). Using a recall-based questionnaire, Caruso, Intelisano, Lupo, and Agnello (2001) showed efficacy of sildenafil in premenopausal FSAD women. Ito, Trant, and Polan (2001) showed efficacy of ArginMax™ using a recall-based questionnaire in women who were not diagnosed with FSAD. Other FSAD studies have only shown positive results in in-clinic models with visual sexual stimulation (Islam et al., 2001; Rosen, Phillips, Gendrano, & Ferguson, 1999; Sipski, Rosen, Alexander, & Hamer, 2000; VIVUS, 2001). It should also be noted that Zestra for Women produced significant beneficial effects in normal women as well as in FSAD women. No efficacy variable showed a deleterious change in either subject group. Subset analysis of efficacy responses in SSRI-using women versus non-SSRI-using women showed that Zestra for Women eliminated the sexual side effects of this class of antidepressants. This is the first report of a product that has achieved these results.

It is interesting to note that results from the diary (FSEP), from the GAQ, and from the QCTS correlated well with each other, but results from the FSFI and from the FSDS appeared to only be weakly supportive, particularly in the normal subjects. Both the FSFI and the FSDS are non-product-specific recall questionnaires. Within the design of the current study, each subject had only five exposures to placebo and five exposures to Zestra over treatment periods of 2–3 weeks. This may have been insufficient time to allow solidification of new attitudes. This raises questions about how to design studies that allow adequate treatment period durations and numbers of exposures. In sum, the half-life of an attitude is a critical concern.

There has been reluctance among researchers to include consumer-testing questions in clinical trials because of questions regarding the impurity of "commercial issues." Yet, the ultimate satisfaction of the end users of products under development should be a vital concern of those who are responsible for these trials. The consumer-testing questions used in this study supported the other efficacy results and specifically addressed how much the subject valued the treatment. In some ways, this is the inverse of a bother index, the success of a product will depend on the users' willingness to purchase and use the product. The subjects in this study indicated that they valued this product.

This study examined the effects of Zestra for Women in only twenty women, and thus it could be criticized as not being generalizable. In our experience, small efficacy studies with strong changes with high significance levels in primary and secondary variables are uniformly confirmed in subsequent larger trials. The mathematics of inferential statistics adjusts for small sample sizes to limit Type I errors. On the other hand, the probability of a Type II error is large in a small study. However, this did not occur in the current study. The most serious limitation of a small clinical study is an underestimation of the AEs. Only adverse events of high incidence can be detected in a small study. The incidence of AEs in this study that can be attributed to the test article was 15% and consisted of mild burning sensations in the genitalia that subsided without treatment in 5 to 30 min.

CONCLUSIONS

Zestra for Women was well tolerated under these conditions of use. It also improved level of desire, satisfaction with level of sexual arousal, level of sexual arousal, genital sensation, sexual pleasure, ability to have orgasms, and enhancement of sexual experiences in normal and FSAD women while eliminating the undesirable sexual side effects of SSRI antidepressants in women.

REFERENCES

Andersson, K. E., & Stief, C. G. (1997). Neurotransmission and the contraction and relaxation of penile erectile tissues. *World Journal of Urology, 15*(1), 14–20.

Basson, R., Berman, L., Burnett, A., Derogatis, L., Ferguson, D., Fourcroy, J., Goldstein, I., Graziottin, A., Heiman, J., Laan, E., Leiblum, S., Padma-Nathan, H., Rosen, R., Segraves, K., Segraves, R. T., Shabsigh, R., Sipski, M., Wagner, G., & Whipple, B. (2000). Report of the International Consensus Development Conference on female sexual dysfunction: Definitions and classifications. *Journal of Urology, 163*, 888–893.

Caruso, S., Intelisano, G., Lupo, L., & Agnello, C. (2001). Premenopausal women affected by sexual arousal disorder treated with sildenafil: A double-blind, crossover, placebo-controlled study. *British Journal of Obstetrics and Gynecology, 108*, 623–628.

Derogatis, L. (May, 2000). *Female Sexual Distress Scale: A preliminary report.* Paper presented at the American Urological Association Annual Meeting, American Foundation for Urologic Disease.

Dines, K. C., Cotter, M. A., & Cameron, N. E. (1996). Effectiveness of natural oils as sources of gamma-linolenic acid to correct peripheral nerve conduction velocity abnormalities in diabetic rats: Modulation by thromboxane A2 inhibition. *Prostaglandins, Leukotrienes, and Essential Fatty Acids, 55*(3), 159–75.

Ferguson, D. M. (2002). Clinical trial development in female sexual dysfunction. *Journal of Sex & Marital Therapy, 28* (Suppl.), 77–83.

Islam, A., Rosen, R., Phillips, N., Ferguson, D., Mitchel, J., Ayers, C., & Yeager, J. (2001). Topical alprostadil in the treatment of female sexual arousal disorder. A pilot study. *Journal of Sex & Marital Therapy, 27,* 531–540.

Ito, T. Y., Trant, A. S., & Polan, M. L. (2001). A double-blind placebo-controlled study of ArginMax, a nutritional supplement for enhancement of female sexual function. *Journal of Sex & Marital Therapy, 27,* 541–549.

Rosen, R. C., Phillips, N. A., Gendrano, N. C., & Ferguson, D. M. (1999). Oral phentolamine and female sexual arousal disorder. A pilot study. *Journal of Sex & Marital Therapy, 25,* 137–144.

Rosen, R., Brown, C., Heiman, J., Leiblum, S., Meston, C., Shabsigh, R., Ferguson, D., & D'Agostino, R. (2000). The Female Sexual Function Index (FSFI). A multidimensional self-report instrument for the assessment of female sexual function. *Journal of Sex & Marital Therapy, 26,* 191–208.

Sipski, M. L., Rosen, R. C., Alexander, C. J., & Hamer, R. M. (2000). Sildenafil effects on sexual and cardiovascular responses in women with spinal cord injury. *Urology, 55,* 812–815.

Teng, C. M., Lin, C. H., Ko, F. N., Wu, T. S., & Huang, T. F. (1994). The relaxant action of osthole isolated from Angelica pubescens in guinea-pig trachea. *Naunyn Schmiedeberg's Archive Pharmacologie, 349*(2), 202–208.

U.S. Food and Drug Administration (2000). *Guidance for industry, female sexual dysfunction: Clinical development of drug products for treatment.* Rockville, MD: U.S. Department of Health and Human Services, Food and Drug Administration, Center for Drug Evaluation and Research (CDER).

VIVUS (2001). Press release. VIVUS announces positive results in Phase II trial evaluating ALISTA™ for the treatment of female sexual arousal disorders. Mountain View, CA: VIVUS.